REMARKS/ARGUMENTS

Claim Amendments

By present amendment, claim 18 has been amended so that it depends on claim 16. This amendment corrects antecedent inconsistencies and in no way alters the scope of claim 18.

The claim amendment has been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants submit that no new matter has been added to the claims as a result of these amendments and their entry is respectfully requested. The Applicants reserve the right to file the canceled subject matter in divisional patent applications.

The Official Action dated October 18, 2005 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Objections

35 U.S.C. §101

The Applicants acknowledge and appreciate the Examiner's withdrawal of the objection to claims 1-60 under 35 U.S.C. §101.

Claim Informalities

The Applicants acknowledge and appreciate the Examiner's withdrawal of the claim objections outlined in the previous Office Action (Paper No. 0405).

35 U.S.C. §112

The Applicants acknowledge and appreciate the Examiner's withdrawal of the objections to claims 1-61 and 68 under 35 U.S.C. §112, second paragraph.

35 U.S.C. §102(g)

The Applicants acknowledge and appreciate the Examiner's withdrawal of the objection to claim 1-60 under 35 U.S.C. §102(g).

37 CFR §1.75(c)

The Examiner has objected to claim 18 and 20 under 37 CFR §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner contends that claims 18 and 20 recite glycerol, propylene glycol and/or trimethylene glycol that are not supported in claim 17. Claim 18, and accordingly claim 20 dependent thereon, has been amended so that it now depends on claim 16. The Applicants submit that proper antecedent basis for glycerol, propylene glycol and /or trimethylene glycol is found in claim 16 since all of these compounds are an organic diols or polyols. Accordingly, the Examiner's objection has been overcome.

In light of the above, the Applicants request that the Examiner's objection to claim 18 and 20 under 37 CFR §1.75(c) be withdrawn.

35 U.S.C. §102(b)

The Examiner has maintained the objection to claims 40, 48 and 50 under 35 U.S.C. §102(b) as being anticipated by Gill2001 (Chem. Mater. (2001), 13, pages 3404-3421).

As the Examiner has noted, claims 40, 48 and 50 are product by process claims. Claims 40, 48 and 50 are directed to siliceous materials prepared using the methods of claim 1, 41 and 49, respectively, i.e. by combining an organic polyol silane precursor with a water soluble polymer or a compound of Formula I and, in the case of claim 50, a biomolecule of interest. The Examiner contends that:

> Clearly, Gill2001 discloses a siliceous material prepared by hydrolysis/condensation of a poly(glyceryl silicate) in the presence of water soluble polymers to form a templated sol-gel bioencapsulate or an interpenetrating polymer network.

To anticipate claims 40, 48 and 50, Gill2001 must teach every limitation of these claims, i.e. the Examiner must provide evidence that the materials taught in Gill2001 are the same as those claimed in the present application. The Applicants submit that the Examiner has not met this burden.

As mentioned in the Applicants' previous response, the only place in Gill2001 where it is specifically mentioned that a water soluble polymer is combined with a sol gel solution is on page 3410, 1st column. There is no teaching in Gill2001 that the sol gel solution includes an organic polyol silane precursor. The materials prepared using the methods of the preparation all involve the use of an organic polyol silane precursor. These materials will all comprise residual organic polyol which helps to stabilize entrapped biomolecules. Since the materials prepared as described in Gill2001 cannot be said to contain residual organic polyol, they do not meet all of the limitations of claims 40, 48 and 50 and therefore Gill2001 does not anticipate these claims.

In light of the above, the Applicants request that the Examiner's objection to claims 40, 48 and 50 under 35 U.S.C. §102(b) be withdrawn.

35 U.S.C. §103(a)

The Examiner has maintained his objection to claims 1-5, 8-10, 38, 40-45 and 47-48 under 35 U.S.C. §103(a) as being obvious over Nakanishi688 (US 5,009,688) in view of Gill (J. Am. Chem. Soc., (1998), 120, 8587-8598). The Applicants, once again, respectfully traverse this objection.

According to MPEP §2143,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Further

> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure.

Nakanishi688 does not teach or suggest the use of compounds of Formula I in methods for preparing siliceous materials accordingly Nakanish688 is only relevant to the present invention in respect of the use of water soluble polymers as an additive in such methods.

Nakanishi688 teaches a method of preparing siliceous materials by hydrolyzing and condensing an alkoxysilane, or an oligomer thereof, in the presence of water soluble organic polymer. As stated in column 1, lines 55-57, of Nakanishi688, the object of the method described therein is to:

> provide a process for producing porous ceramics with a pore diameter of a micron order and having a narrow pore size distribution.

Nakanishi688 does not mention or suggest the application of the materials produced therein in chromatography (see column1, lines 8-10, for a list of potential applications proposed by Nakanish688).

Gill describes methods of entrapping biomolecules in siliceous materials prepared from polyol silicates, in particular, polyglyceryl silicate (PGS). The parameters of interest to Gill include percent entrapment of the biomolecule (the higher the better) and maintenance of activity (thus the need for mild conditions). The pore structure of the PGS derived materials produced by Gill are described as mesoporous (see page 8588, column 2, line 20, with pore sizes ranging from 10.4 nm to 16.4 nm - see Table 1). Gill does not mention or suggest the application of the materials produced therein in chromatography (see page 8594 of Gill for a list of potential applications proposed by Gill).

The Examiner contends that

> [a]lthough Gill does not explicitly [teach] the use of Applicants' polyol silane precursor, as mentioned above, Gill does teach the advantage of using glyceryl groups as compared to lower alkyloxy groups for making sol gel product. Furthermore, note that Gill's poly(glyceryl silicate) is an intermediate when Applicants' polyol silane precursor is partially hydrolyzed/condensed. Therefore, one of ordinary skill in the art would know to replace Nakanishi688's lower alkoxy groups with glycerol groups.

As noted throughout the present application, in particular on page 12, lines 1-4, the method of the present invention provides biomolecule compatible monolithic siliceous materials having a *bimodal meso/macroporous* structure when polyol silanes are combined with water soluble polymers. Such materials are useful in *chromatographic* applications and are especially amenable to the entrainment of biomolecules.

Neither Nakanishi688 or Gill teach methods of preparing bimodal silica having a meso/macroporous structure. Neither document even remotely suggests the possibility or advantages of doing so. The Applicants therefore ask the Examiner why a person skilled in the art, faced with the problem solved by the present invention, would even look to the teachings of Gill or Nakanishi688 to find the answer? Certainly the requisite motivation for success is lacking since neither document teaches that a bimodal siliceous material may be prepared using the methods described therein.

Further support for the lack of motivation to modify Nakanishi688 is the fact that modification of any of the conditions used in the method taught in Nakanishi688 is not recommended. See, for example, column 3, lines 18-29, of Nakanishi where it is taught that

> the porous stereostructure of the desired product of the present invention varies depending upon the temperature and pH of the

> reaction system, the molecular weight and the content of the organic polymer and other various conditions influential over the reactivity of the metal alkoxide or its oligomer and over the solubility of organic polymer. [...] However, *so long as the above-mentioned conditions are the same,* the desired product having substantially the same structure such as the same pore size can be obtained with high reproducibility. [Emphasis added]

The above passage serves to illustrate how varying the reaction conditions described in Nakanishi688, including "various conditions influential over the reactivity of the metal alkoxide" will have unpredictable effects on the reproducibility of the method. This is indicative of a lack of expectation of success if Nakanishi688 were to be modified as suggested by the Examiner. As noted above, expectation of success is a critical factor in any obviousness analysis (see MPEP 2143.02).

Still further, the Applicants submit that Nakanishi688 does not teach the desirability of the use in any form of biologically compatible materials in the preparation of silica. Harsh conditions, including alcoholic solvents and calcination, are utilized in critical steps in the preparation of the silica materials described in Nakanishi688. Calcining, which involves heating the gel to temperatures of from 800 °C to 1000 °C, would decompose any biomolecule of interest and is taught in Nakanishi688 (at column 3, lines 30-35) to be essential if the materials produced are to be useful:

> The porous gel formed as an intermediate produce may be used as it is. However, it swells in water and is poor in the mechanical strength, and therefore its use is rather limited. The above-mentioned porous gel can be converted to a SiO_2 type porous ceramic having improved mechanical strength when calcined.

The Applicants submit, therefore, that this provides further support that a person skilled in the art would not have been motivated to modify Nakanisi688 to arrive at the present invention. The Applicants submit that a person skilled in the art would not even have considered Nakanishi688 as a relevant reference since it requires non-biomolecule compatible methods to obtain a useful product.

Finally, the Examiner's contention that Gill teaches the advantage of using glyceryl groups as compared to lower alkyloxy groups and therefore a person skilled in the art would know to replace Nakanishi688's lower alkoxy groups with glycerol groups does not take full consideration of the method of the present invention as it compares to that in Gill. In order to arrive at the present invention, Gill would not only have to be modified to include the use of water soluble polymers and compounds of Formula I but would also have to be modified to replace the polyol silicate precursors with the polyol modified silanes of the present invention. The Applicants submit that, contrary to the Examiner's contention, the polyol silicate precursors of Gill and the polyol silanes of the present invention are fundamentally different entities having different reactivities that result in significantly different products in condensation and polymerization reactions used to prepare sol gels. In support of this, the Applicants have submitted herewith evidence in form of a declaration under 37 CFR §1.132, *showing that Gill's polyglyceryl silicate (PGS) does not produce bimodal meso/macroporous siliceous materials when used in combination with a water soluble polymer in the methods as claimed in the present application.*

Gill at no point suggests the preparation or use of a polyol modified silane precursor. Further, it is plainly clear from the above discussion and attached declaration that there are differences in the reactivity of polyol silicates and polyol silanes. These differences are significant since the Applicants have shown that polyol silicates, specifically Gill's PGS, cannot be used for the formation of bimodal siliceous materials advantageous for chromatographic applications as per the method of the present application. This would not have been known to a person skilled in the art from the teaching of Gill since Gill does not teach the use of polyol silanes as precursors for silica gel, let alone in combination with water soluble polymers. Further, as mentioned above, Gill does not describe methods of forming bimodal siliceous materials.

It is clear that the Examiner has not met his burden to find motivation to modify the prior art references and thereby render the present invention obvious. In particular, there is absolutely no motivation or suggestion for a person skilled in the art to

substitute the polyol silanes of the present invention for the alkoxy silanes in the method of Nakanishi688, in particular in view of Gill. Neither document relates to the formation of bimodal siliceous materials, Nakanishi688 does not relate to a biomolecule compatible method and Gill's polyol silicates do not work in the method of the present invention.

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not Applicant's specification. It is, therefore, improper to:

> [use] that which the inventor taught against its teacher. ***In re Lee*, 277 F.3d at 1343** citing ***W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir 1988).**

The Applicants submit that their method of preparing biomolecule compatible bimodal siliceous materials was neither known nor suggested in the cited art.

Since in all of claims 1-5, 8-10, 38, 40-45 and 47-48, the use of organic polyol silanes is claimed, and, since neither Nakanishe875 or Gill teach the use of such precursors, let alone the advantages of using such precursors (including bimodal pore distribution in the resulting sol), in methods of preparing siliceous materials, the Applicants submit that the subject matter of these claims is not obvious in light of Nakanishi688 in view of Gill.

In light of the above arguments, the Applicants request that the Examiner's objection to claims 1-5, 8-10, 38, 40-45 and 47-48 under 35 U.S.C. §103(a) be withdrawn.

The Examiner has maintained the objection to claims 1-5, 8-10, 40-45, 47-52, 54-55 and 56 under 35 U.S.C. §103(a) as being obvious over Nakanishi875 (US 5,624,875) in view of Gill (J. Am. Chem. Soc., (1998), 120, 8587-8598). The Applicants respectfully traverse this objection.

According to MPEP §2143,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Further

> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure.

Nakanishi875 does not teach or suggest the use of compounds of Formula I in methods for preparing siliceous materials accordingly Nakanish875 is only relevant to the present invention in respect of the use of water soluble polymers as an additive in such methods.

Nakanishi875 teaches the advantages of using a siliceous material having bimodal pore (meso/macroporous) distribution in chromatographic applications, however it is important to note that bimodal silica was not obtained by simply combining an alkoxysilane, or polymer thereof, with a water soluble polymer under sol gel reaction conditions. The sol gel reaction in the method taught in Nakanishi875 simply provides a wet bulk having phase domains rich in solvent which convert to macropore spaces (see column 2, lines 14-17). To obtain the mesoporous structure, the resulting bulk gel has to be immersed in solutions of so-called "matrix dissolving agents" (see column 2, lines 32-44). It is important to note that the step of treating the gel with a matrix dissolving agent is essential for obtaining the mesoporous structure:

> This step is **essential** for creating the sharply distributed mesopores. (column 2, lines 43-44, emphasis added)

Accordingly, Nakanishi875 does not teach a method of preparing bimodal siliceous materials under sol gel reaction conditions. Further, Nakanishi875 does not, in any way, teach or suggest the use of organic polyol silane precursors in this method.

Gill describes methods of entrapping biomolecules in siliceous materials prepared from polyol silicates, in particular, polyglyceryl silicate (PGS). The parameters of interest to Gill include percent entrapment of the biomolecule (the higher the better) and maintenance of activity (thus the need for mild conditions). The pore structure of the PGS derived materials produced by Gill are described as mesoporous (see page 8588, column 2, line 20, with pore sizes ranging from 10.4 nm to 16.4 nm - see Table 1). Gill does not mention or suggest the application of the materials produced therein in chromatography (see page 8594 of Gill for a list of potential applications proposed by Gill).

The Examiner contends that

> [a]lthough Gill does not explicitly [teach] the use of Applicants' polyol silane precursor, as mentioned above, Gill does teach the advantage of using glyceryl groups as compared to lower alkyloxy groups for making sol gel product. Furthermore, note that Gill's poly(glyceryl silicate) is an intermediate when Applicants' polyol silane precursor is partially hydrolyzed/condensed. Especially, Nakanishi875 teaches that glycerol gives the best result among other polyols as components for the pore forming phase. (col. 5, lines 57-60), and when a silane containing glyceryl is used in Nakanish875's method, during hydrolysis condensation, the desirable glycerol will be liberated. Therefore, in view of the various advantages mentioned above, one of ordinary skill in the art would know to replace Nakanishi875's lower alkoxy groups with glycerol groups.

As noted throughout the present application, in particular on page 12, lines 1-4, the method of the present invention provides biomolecule compatible monolithic siliceous materials having a *bimodal meso/macroporous* structure when polyol silanes are combined with water soluble polymers. Such materials are useful in

chromatographic applications and are especially amenable to the entrainment of biomolecules.

Nakanishi875 teaches a method of preparing bimodal meso/macroporous silica, however this method requires that the initially formed macroporous sol gel be immersed in solutions of so-called "matrix dissolving agents" to create the mesopores (see above). Such a step would have obvious disadvantages when there are sensitive biomolecules entrapped within the silica. The matrix dissolving agents taught in Nakanishi875 include basic substances such as ammonia or sodium hydroxide and acidic substances such as hydrogen fluoride (see column 4, line 66, to column 5, line 10). The Applicants submit that a person skilled in the art would know that all of these substances would be detrimental to the activity of most biomolecules. Still further, the Applicants submit that Nakanishi875 does not teach the desirability of the use in any form of biologically compatible materials in the preparation of silica. Harsh conditions, including alcoholic solvents, mineral acids and heat treatment, are utilized in the preparation of the silica materials described in Nakanishi875. The Applicants submit, therefore, that this provides support that a person skilled in the art would not have been motivated to modify Nakanisi688 to arrive at the present invention. The Applicants submit that a person skilled in the art would not even have considered Nakanishi875 as a relevant reference since it requires non-biomolecule compatible methods to obtain a useful product.

Finally, the Examiner's contention that Gill teaches the advantage of using glyceryl groups as compared to lower alkyloxy groups and this, along with the fact that Nakanisi875 teaches that glycerol is advantageous in the pore forming phase, would lead a person skilled in the art to replace Nakanishi875's lower alkoxy groups with glycerol groups, does not take full consideration of the method of the present invention as it compares to that in Gill. In order to arrive at the present invention, Gill would not only have to be modified to include the use of water soluble polymers and compounds of Formula I but would also have to be modified to replace the polyol silicate precursors with the polyol modified silanes of the present invention. The Applicants submit that,

contrary to the Examiner's contention, the polyol silicate precursors of Gill and the polyol silanes of the present invention are fundamentally different entities having different reactivities that result in significantly different products in condensation and polymerization reactions used to prepare sol gels. In support of this, the Applicants have submitted herewith evidence in form of a declaration under 37 CFR §1.132, *showing that Gill's polyglyceryl silicate (PGS) does not produce bimodal meso/macroporous siliceous materials when used in combination with a water soluble polymer in the methods as claimed in the present application.*

Gill at no point suggests the preparation or use of a polyol modified silane precursor. Further, it is plainly clear from the above discussion and attached declaration that there are differences in the reactivity of polyol silicates and polyol silanes. These differences are significant since the Applicants have shown that polyol silicates, specifically Gill's PGS, cannot be used for the formation of bimodal siliceous materials advantageous for chromatographic applications as per the method of the present application. This would not have been known to a person skilled in the art from the teaching of Gill since Gill never suggests the use of polyol silanes as precursors for silica gel, let alone in combination with water soluble polymers. Further, as mentioned above, Gill does not describe methods of forming bimodal siliceous materials.

It is clear that the Examiner has not met his burden to find motivation to modify the prior art references and thereby render the present invention obvious. In particular there is absolutely no motivation or suggestion for a person skilled in the art to substitute the polyol silanes of the present invention for the alkoxy silanes in the method of Nakanishi875, in particular in view of Gill. Neither document relates to the formation of bimodal siliceous materials using only sol gel chemistry, Nakanishi875 does not relate to a biomolecule compatible method and Gill's polyol silicates do not work in the method of the present invention.

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not Applicant's specification. It is, therefore, improper to:

> [use] that which the inventor taught against its teacher. ***In re Lee*, 277 F.3d at 1343** citing ***W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir 1988).**

The Applicants submit that their method of preparing biomolecule compatible bimodal siliceous materials was neither known nor suggested in the cited art.

Since all of the claims of the present application require the use of an organic polyol modified silane precursor and since, neither Nakanishe875 or Gill teach the use of such precursors, let alone the advantages of using such precursors (including bimodal pore distribution in the resulting sol), in methods of preparing siliceous materials, the invention as claimed in claims 1-5, 8-10, 40-45, 47-52, 54-55 and 56 of the present application are not obvious in light of Nakanishi875 in view of Gill.

In light of the above arguments, the Applicants request that the Examiner's objection to claims 1-5, 8-10, 40-45, 47-52, 54-55 and 56 under 35 U.S.C. §103(a) be withdrawn.

The objection to Claim 38 under 35 U.S.C. §103(a) as being obvious over Nakanishi875 (US 5,624,875) in view of Gill (J. Am. Chem. Soc., (1998), 120, 8587-8598) and as evidenced by Barkin (US 3,374,103) has been maintained. The Applicants respectfully traverse this objection.

Claim 38 depends on claim 1 and specifies that the conditions suitable for the hydrolysis and condensation of the precursor to a siliceous material include a pH in the range of about 4-11.5 in aqueous solutions and with optional sonication to assist in dissolution. The Examiner has combined the teaching in Barkin that the pKa of acetic acid is 4.76 with the teaching in Nakanishi875 that hydrolysis/condensation of a silicone alkoxide is carried out in a 0.001 mol/l aqueous solution of acetic acid to conclude that the pH of the reaction medium in Nakanish875 should fall with in the range claimed in claim 38 of the present application.

The Applicants submit that the arguments provided above that teachings in Nakanish875 in view of Gill do not render the claims in the present application obvious (in particular claim 1 upon which claim 38 depends), apply to the Examiner's objection to claim 38 described above.

Accordingly, the Applicants submit that claim 38 is not obvious over Nakanishi875 (US 5,624,875) in view of Gill (J. Am. Chem. Soc., (1998), 120, 8587-8598) and as evidenced by Barkin (US 3,374,103) and request that the Examiner's objection to this claim under 35 U.S.C. §103(a) be withdrawn.

The Examiner has objected to claims 53 and 57-61 under 35 U.S.C. §103(a) as being obvious over Nakanishi875 (US 5,624,875) in view of Gill (J. Am. Chem. Soc., (1998), 120, 8587-8598). The Applicants respectfully traverse this objection.

The Examiner contends that:

> it would have been obvious to one of ordinary skill in the art at the time of the invention was made to encapsulate Gill's biomolecules in Nakansishi875 in view of Gill's matrix.

As argued above, the Applicant submits that the matrixes prepared in Gill, using polyol silicates as silica precursors, are in no way suggestive of the materials prepared using the methods of the present invention since polyol silicates do not work in the method of the present invention. Nakanishi875 goes no further to teach a person how to arrive at the methods of the present invention since Nakanish875 does not teach or suggest using polyol silane precursors. Accordingly, a person skilled in the art could not combine the teachings of Gill and Nakanishi to arrive the methods claims in claims 53 and 57-61 of the present invention.

In light of the above arguments, the Applicants request that the Examiner's objection to claims 53 and 57-61 under 35 U.S.C. §103(a) be withdrawn.

The Applicants acknowledge and appreciate the Examiner's indication that claims 6-7, 11-17, 19, 21-37, 46 and 74 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The Applicants acknowledge and appreciate the Examiner's indication that claims 18 and 20 would be allowable if rewritten to overcome claim objections set forth in the Office Action and to include all of the limitations of the base claim and any intervening claims.

The Applicants acknowledge and appreciate the Examiner's indication that claims 39 and 62-73 are allowed.

In view of the foregoing arguments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, the Examiner is invited to contact the undersigned by telephone at (416) 957-1683 at the Examiner's convenience.

Respectfully submitted,

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